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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/732,862
Filing Date: December 10, 2003
Appellant(s): LYONS ET AL.

Edward P. Gamson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 17, 2010, appealing from the Office action mailed March 3, 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

11/508,655 and 09/930,915

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-47 are rejected and pending.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN

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REJECTIONS.” New grounds of rejection (if any) are provided under the subheading “NEW GROUNDS OF REJECTION.”

The rejection of claims 1-46 under obviousness-type double patenting over the claims of 10/805,913, 10/806,006 and 11/507,083 is moot in view of the abandonment of the applications.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant’s brief.

(8) Evidence Relied Upon

- Rudinger, J. *Peptide Hormones*; Ed by J.A. Parsons.
- Metzger *et al.* “Proline-138 is essential for the assembly of hepatitis B virus core protein” J. Gen. Virology, 79:587-590, 1998.
- Pumpens *et al.* “Hepatitis B virus core particles as epitope carriers” Intervirology 38:63-74, 1995.
- Zlotnick *et al.* “Localization of the C terminus of the assembly domain of hepatitis B virus capsid protein: Implications for morphogenesis and organization of encapsidated RNA” PNAS, 94:9556-9561, 1997.
- Page *et al.* WO 01/98333
- Zhang *et al.* “The structure of hepadnaviral core antigens” J. Biological Chemistry, 267(13): 9922-9429, 1992.
- Birkett US Pat. No. 6,231,864.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claims 1-47 were rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the Office action dated March 3, 2010. The rejection is re-iterated herein for convenience.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 USC 112 written description requirement for a generic claim covering several distinct inventions:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Appellant was in possession of the claimed genus... See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

It is also noted that even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. See, *In re Smyth*, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating “where **there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated**, one skilled in the art may be

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found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application.”); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). Thus, when a claim covers a genus of inventions, the specification must provide sufficient written description support for the entire scope of the genus. Support for a genus is generally found where the Appellant has provided a sufficient number of examples so that one skilled in the art would recognize from the specification the scope of what is being claimed, or provided a function and a structure correlating with that function. Moreover, in situations where the operability of species other than those provided is uncertain, additional support is required over that which would be required where greater certainty is present.

1. The claims are directed HBc chimers up to about 600 amino acids which can self assembly into particles (Note: Polymerized HBc proteins form T3 or T4 particles; See Pumpens, left col. p. 64 about HBc particle), wherein the HBc contain a 5% substitutions (mutations) corresponding to a wild type (wt) HBc of SEQ ID No: 1; and one or both cystines at positions 48 (C48) and 107 (C107) is replaced by another residue; wherein the HBc contains heterologous epitopes at N-, immunodominant loop between about 76-85, or /and C-terminus. The scope of the claims encompasses a large number of HBc variants, which contains 5% substitutions (mutations) corresponding to a wild type (wt) HBc of SEQ ID No: 1. The claims require such HBc chimers made from HBc variants can form particles, and has enhanced stability [Claim 25(iii)].

2. In support of the claims, the specification Example 14 shows a few species of HBc chimers comprising two or three mutations in the HBc protein, for example, 7 of 24 chimers in

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Table 13, were able to yield particles; see Table 13 of Example 14, pp. 194 to 195. Of the modified HBc chimers in the above example, however, 17 of the 24 tested lost their ability to form particles. Thus, the specification shows that it is uncertain if HBc chimers containing a 5% substitution frequency in wt HBc of SEQ ID No: 1 can form viral-like particles as can wt HBc, or would the resultant HBc particles have enhanced stability as claimed.

3. The art indicates that the result of peptide modification is, in general, unpredictable. Modification of a peptide by as little as one amino acid can cause a change in conformation, and thus peptide function, that can't be predicted in advance. See Rudinger, J. at page 6. Particularly, Metzger teaches that a single amino acid change, Pro-138 to Gly, prevents self-assembly of the HBc protein into particles (Metzger, J. Gen. Virology, 79:587-590, 1998). Substitution of a single amino acid can result in an unpredictable effect on the assembly of HBc particles. These teachings in the art are consistent with the result shown in the specification Example 14.

4. Although the specification discloses a few species of modified HBc chimers comprising substitutions of C48 and C107 of wt HBc, the specification has also illustrated that most amino acid changes in wt HBc result in an inability to form particles. Given the substantial structural variations and functional uncertainty of forming particles within the genus, a few species of modified HBc chimers is not a representative number of species of the entire genus. The specification has failed to provide an adequate description which amino acid substitutions in the HBc chimers can still form viral-like particles, and has enhanced stability comparing to wt HBc. Consequently, the skilled artisan would reasonably conclude Appellant was not in possession of the claimed HBc chimers containing a 5% substitution frequency of amino acid residues corresponding to wt HBc of SEQ ID NO: 1 resulting in enhanced stability.

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II. Claims 1-47 were rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a HBc chimera of SEQ ID NO: 1, does not reasonably provide enablement for a HBc chimera containing up to about 5% substituted amino acid residues corresponding to wt HBc of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. This rejection was made in the Office action dated January 9, 2008; and was maintained in the office actions dated July 22, 2008, and March 3, 2009. The rejection is re-iterated herein for convenience.

In making a determination as to whether an application has met the requirements for enablement under 35 USC 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors that are considered most relevant are the presence or absence of working examples, the direction or guidance presented, and the nature of the invention.

5. The independent Claims 1, 11, 25 and 47 specify a chimera molecule with up to about 5 percent substituted amino acid residues in the HBc sequence. The scope of claims encompasses a large number of HBc chimeras that contain 5% substitutions variously arranged along the

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sequence of SEQ ID No: 1. Although Appellant has disclosed a few species of HBc mutants C48S/C107S, such as Chimer No. 1775 and 1789 shown in Table 13, are able to form particles, other HBc variants in Table 13 lost their ability to form particles. Thus, the specification shows most changes of amino acids in wt HBc proteins result in inabilities of the HBc variants to form particles. Appellant has not disclosed sufficient species of alternative HBc variants, which contain 5% substitutions of wt HBc and can form stable HBc chimer particles. More importantly, Appellant fails to provide the necessary guidance that would lead one to such molecules. First note, it is stated as substituted and not conservatively substituted. Therefore, it seems more than reasonable to assume that a nonconservative substitution in the amino acid sequence will have a deleterious effect on the conformation of the HBc molecule. Second, even a single substitution can have an unpredictable effect on conformation of the resulting molecule. "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." See Rudinger, J. at page 6. Thus, a single amino acid can create problems resulting from changes in conformation that can't be adequately predicted in advance. Therefore, the specification does not enable those of skill in the art to make the claimed invention commensurate in scope with these claims.

III. Claims 1-6, 8-14, 16-28, 30-42 and 46 were rejected under 35 USC 103(a) as being unpatentable over Pumpens *et al.* (1995, Intervirology, Vol. 33, pp. 63-74), in view of Zlotnick, *et al.* (1997, PNAS, Vol. 94, pp. 9556-9561) and Zhang (1992, J. Biological

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Chemistry, Vol. 267 (13): pp. 9922-9429). This rejection was made in the office action dated November 17, 2006, and maintained in the Office action dated May 15, 2007, January 9, 2008, July 22, 2008, and March 3, 2009. The rejection is re-iterated herein for convenience.

6. Claims 1-6, 8-14, 16-28, 30-42 and 46 read on HBc chimers up to about 380 or 600 amino acids which can self assemble into particles, wherein one or both cystines at positions 48 (C48) and 107 (C107) of HBc is replaced by another residue, and one to three cystein residues toward the C-terminus; wherein the HBc contains heterologous epitopes at N-, immunodominant loop between about 76-85, or /and C-terminus, wherein the HBc contain a 5% substitutions (mutations) corresponding to a wild type (wt) HBc of SEQ ID No: 1.

7. Pumpens teaches immunogenic compositions and vaccines using recombinant HBc chimer molecules of a variety of lengths up to about 380 or 600 amino acid residues in length. Pumpens teaches that both full-length HBc and C-terminal truncated HBc Δ can form capsid particles. The HBc and HBc Δ chimers can carry B-cell and T-cell epitopes at their N-terminus, C-terminus or at internal immunodominant loop sites at positions 76 through 85 (See Figure 1 and Tables 1 through 3). Pumpens also teaches such chimers can contain two epitopes at both the immunodominant loop and C-terminus (see Table 2). These chimers contain an HBc sequence of at least about 130 of the 150 N-terminal amino acid residues of the HBc molecule (See for instance Fig. 1, pg. 64) that include a peptide-bonded heterologous epitope (Table 1, page 66) or a heterologous linker residue which code for epitope present in the HBc immunodominant loop at positions 76 through 85 (see page 69, col. 1, last paragraph). Pumpens discloses that HBc chimeras with C-terminal truncations are capable of self-assembly and do not bind or 'pack' nucleic acids in their capsid particles (page 67, col. 1).

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8. Pumpens does not explicitly teach replacing one or both cysteine residues at positions 48 and 107 by another residue and adding a C-terminal cysteine residue to achieve the stabilizing effect.

9. Zlotnick teaches that the protamine domain (residues 150-183) at the C-terminus of HBc is required for packaging viral RNA and deletion of this region results in the generation of HBcΔ virus capsids free of RNA (abstract; pg. 9556, col.1; pg. 9560, col. 2). Zlotnick also teaches that the addition of a single heterologous cysteine at the C-terminus of HBcΔ can stabilize the virus capsid dimers after deletion of its protamine domain 150-183. Zlotnick shows that the Cp*150 capsids, in which three native Cys48, Cys61 and Cys107 are replaced by three Ala, and a single heterologous cysteine is added to position 150 after deletion of its protamine domain 150-183, forms disulfide dimers at pH 7.5 and 9, but not Cys-free Cp*149 (see Figure 2, right column 9557). Zlotnick has shown that unlike the Cys-free Cp*149 capsids, the Cp*150 capsids, is more stable than not Cys-free Cp*149, and is resistant to dissociation by 3.5 M Urea, suggesting that disulfide bond formation by Cp*150 can promote capsid assembly (Results and Discussion, paragraph 1 and 2, p. 9558).

10. Zheng teaches the function of native cysteines in the formation of HBc particles. Zheng teaches that the intra-chain disulfide bonds are not essential for core particle formation, but inter-chain disulfide bonds are involved in formation of HBc capsid dimers with the identical residues of another monomer. Zheng teaches that the native Cys107 is buried within the particle structure and is not involved in HBc capsid formation. The native Cys61 and Cys183 are always, and Cys48 is partially, involved in inter-chain disulfide bonds with the identical residues of another monomer.

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11. It would have been obvious to one of ordinary skill in the art to make a C-terminal truncated HBcΔ chimera containing an epitope at its N-terminus, immunodominant loop, or C-terminal region, or containing two epitopes in these areas, in which native Cys48 and/or Cys107 are conservatively replaced by another residue, and a heterologous cysteine is added at the C-terminus of HBcΔ. One of ordinary skill in the art would have been motivated to do so and would have reasonable expectation of success that such HBcΔ chimera would be capable of incorporating foreign epitopes, and be free of viral nucleic acid binding and with enhanced stability, given the knowledge HBcΔ chimeras are free of viral RNA, while still capable of self-assembly as taught by Zlotnick, and a various of HBcΔ chimera containing an epitope(s) at its N-terminus, immunodominant loop, or/and C-terminal region have been successfully made as taught by Pumpens, given the knowledge that the addition of a heterologous cysteine residue to an HBcΔ C-terminal truncation results in dimer formation and enhanced stability, as taught by Zlotnick, and also given the knowledge that native Cys48 and Cys107 are not essential for HBc dimer formation, as taught by Zhang. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

IV. Claims 1-6, 8-28, and 30-46 were rejected under 35 USC 103(a) as being unpatentable over Page, *et al* (WO 01/98333 A2), Birkett (6,231,864), both in view of Zhang (1992, *J. Biological Chemistry*, 267 (13): 9922-9429). This rejection was made in the Office action dated November 17, 2006, and maintained in the Office action dated May 15, 2007, January 9, 2008, July 22, 2008, and March 3, 2009. The rejection is re-iterated herein for

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convenience.

12. Claims 1-6, 8-14, 16-28, 30-42 and 46 are summarized in Para 6 above. Moreover, the said HBc chimera contains a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop between amino acid residues 76 and 85 (Claims 43-45).

13. Page teaches the use of HBc Δ as a vehicle for the presentation of epitopes. Page teaches a modified HBc Δ chimera where one or more of the four arginine repeats responsible for RNA binding at the C-terminus (between 150-180) have been deleted followed by the addition/retention of a C-terminal cysteine residue. Page teaches “[t]he removal of the arginine repeats residues the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a disulphide bond which in the native structure is important for the formation of a stable particle.” (See page 2). Page teaches the addition of epitopes at the C-terminus, in and around the e1 loop from roughly residues 68 to 90 (i.e. the immunodominant loop) and the N-terminus (See page 10). The epitopes may be B-cell epitopes or T-cell epitopes (See pages 11 and 26). The recombinant core antigen may contain multiple heterologous epitopes. (See pages 11 and 26) Moreover, these epitopes may be different epitopes from the same organism or even multiple copies of the same epitope within the core molecule. Epitopes may be conformational or linear. Epitopes may range widely in size, which would correspondingly affect the overall size of the chimera. Page teaches that the protein self-assembles into particles which may closely resemble the particles formed by native HBcAg (See page 9).

14. Page does not explicitly teach incorporating a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop between amino acid residues 76 and 85 (Claims 43-45); and does not teach replacing one or both cysteine residues at positions 48

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and 107 by another residue.

15. Birkett teaches incorporating a heterologous linker residue for a conjugated epitope present in the immunodominant loop of HBc. Birkett teaches introducing a lysine residue at the HBc immunodominant loop between positions 76-85 for a conjugated epitope (whole document, particularly see Abstract, Example 1 and claims).

16. The relevance of Zhang is set forth *supra*.

17. It would have been obvious to one of ordinary skill in the art to make a C-terminal truncated HBcΔ chimera containing an epitope(s) at its N-terminus, immunodominant loop, or/and C-terminal region, wherein a heterologous linker residue for a conjugated epitope is present in the HBc immunodominant loop between amino acid residues 76 and 85, wherein a cysteine is added at their C-terminus, and native Cys48 and/or Cys107 are conservatively replaced by another residue. One of ordinary skill in the art would have been motivated to do so and would have reasonable expectation of success, given the knowledge that HBcΔ chimeras are capable of incorporating foreign epitope(s) at their N-terminus, immunodominant loop, or/and C-terminal region, and also capable of forming viral RNA-free capsid, as taught by Page, given the knowledge that addition/retention of C-terminal cysteines allows the formation of a stable HBcΔ dimer particle as taught by Page, given the knowledge that HBc chimera containing a chemically-reactive linker residues for a conjugated hapten at their immunodominant loop have been successfully made, as taught by Birkett, and also given the knowledge that native Cys48 and Cys107 are not essential for HBc dimer formation, as taught by Zhang. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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V. Claims 1-46 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) Claims 1-78 of 09/930,915; (2) Claims 1-53 of 10/787,734 (now US Pat. 7,361,352); (3) Claims 47-85 of 11/508,655. The rejection over the claims of 10/805,913, 10/806,006 and 11/507,083 is moot in view of the abandonment of the applications.

18. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant Claims 1-69 are drawn to the same subject matter, e.g., recombinant chimer HBC protein molecules that have C-terminal cysteines, self-assemble into particles, and have improved particle stability, as are Claims 1-46 of 10/732,862, differing only in scope.

VI. Claims 1-6, 8-28, and 30-46 were rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Page, *et al* (WO 01/98333 A2) and Zheng (1992, J. Biological Chemistry, Vol. 267 (13): pp. 9922-9429)

19. Claims 1-9 of '864 teach a modified hepatitis B core protein comprising a chemically reactive amino acid residue, preferably in an immunodominant region of the nucleocapsid protein. The modified hepatitis B core protein or its aggregated nucleocapsid protein particles can be pendently linked to a hapten to form a modified nucleocapsid conjugate. The modified hepatitis B core protein can also be modified to include a T cell epitope.

20. Page teaches the use of HBc Δ as a vehicle for the presentation of epitopes. Page teaches a modified HBc Δ chimer where one or more of the four arginine repeats responsible for RNA

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binding at the C-terminus (between 150-180) have been deleted followed by the addition/retention of a C-terminal cysteine residue.

21. Zheng teaches the function of native cysteines in formation of HBc particles. Zheng teaches that the intra-chain disulfide bonds are not essential for core particle formation, but inter-chain disulfide bonds are involved in formation of HBc capsid dimers with the identical residues of another monomer. Zheng also teaches that the native Cys107 is buried within the particle structure and is not involved in HBc capsid formation. The native Cys61 and Cys183 are always, and Cys48 is partially, involved in inter-chain disulfide bonds with the identical residues of another monomer.

22. One of ordinary skill in the art would have been motivated to combine the teachings of Birkett with that of Page and Zheng in order to make an HBc Δ molecule that could present an epitope *via* a side-chain. One would have been motivated to do so, and would have had a reasonable expectation of success, given the knowledge that both HBc and HBc Δ have been successfully used for displaying heterologous epitopes on HBc particles, as taught by Birkett and Page, and given the knowledge that methods for operatively linking individual haptens to polypeptides through an amino acid residue side chain to form an immunogenic conjugate are well known in the art, as taught by Birkett, see e.g. col. 13 and 14, and also given the knowledge that native Cys48 and Cys107 are not essential for HBc dimer formation, as taught by Zheng. Therefore, the instant claims would have been *prima facie* obvious over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Page and Zheng.

(10) Response to Argument

23. Appellant has presented three arguments in traverse of this rejection. Appellant argues (1) that the chimer of Table 13 of the specification are not reflective of the current claims, because none of the 24 in Table 13 contains all of the limitations recited in the claims, such as having a heterologous epitope, having C48 and/or C107 substitutions, and having 1-3 cysteines on both or either terminus. Appellant argues (2) that the instability of HBc variants to form particles is due to the nature of epitope peptides. As such, arguments as to lack of written description based on the data of Table 13, which molecules are not reflective of the present claims, are irrelevant. Therefore, this rejection should be withdrawn. (Appeal Brief, Para 1, p. 15 to first Para of p. 17)

24. Appellant's arguments should not be found persuasive for following reasons: First, Appellant's argument (1) is not accurate because HBc V16(C48S/C107S) chimer recited in Table 13 contain all of the limitations recited in the claims, such as having a heterologous epitope, having C48 and/or C107 substitutions, and having one cysteines at the C-terminus. It is noted that a series of HBc V16(C48S/C107S) chimer are recited in Table 13, including Chimer 1794 V16(C48S/C107S).βAm; Chimer 1775 V16(C48S/C107S).ASP-1; Chimer 1780 V16(C48S/C107S).PA; and Chimer 1789 V16(C48S/C107S).IA(M2)2C/2S. The specification provides the following description of the structural features of "V16" chimer: "Modified HBc149 (V2 and V16)..., were constructed using PCR. (The plasmid accepting inserts between D78 and P79 and truncated to V149 was named V2, **the same plasmid with an additional cysteine following V149 was named V16**, ..."; see page 140, para 2, line 1-7; (PG Pub Para [0412]). Based on this description, "**V16**" represents an HBcΔ comprising an additional Cys at its C-terminus (HBcΔ+C). "**V16 chimer**" has an HBcΔ+C core structure and further comprising a foreign epitope inserted between amino acids D78 and P79 at the immunodominant loop of HBcΔ. "**HBc V16(C48S/C107S) chimer**" means a V16 chimer further comprises substitution of both Cys48 and Cys107 with serine (S). Specifically, for example, Chimer 1794 V16(C48S/C107S).βAm means a HBc chimer, which comprises substitution of both Cys48 and

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Cys107 with serine (S), an additional cysteine at its *C*-terminus (HBcΔ+C), and a heterologous epitope of βAm inserted between amino acids D78 and P79 at the immunodominant loop of HBcΔ. Like Chimera 1794 V16(C48S/C107S).βAm, the other Chimera 1775 V16(C48S/C107S).ASP-1; Chimera 1780 V16(C48S/C107S).PA; and Chimera 1789 V16(C48S/C107S).IA(M2)2C/2S also possess each and every structural limitation recited in the claims, such as having a heterologous epitope, having C48 and/or C107 substitutions, and having one cysteine at the *C*-terminus. Thus, Appellant's argument (1) is not accurate. Since Table 13 appears to be the only Table in the specification that shows the characterization of assembled epitope-carrying chimeras, the data shown in Table 13 is directly relevant to the teachings of the claimed chimeras. Thus Appellant's argument (1) about Table 13 should not be found persuasive.

25. Secondly, regarding Appellant's argument (2), the effect of epitope peptide inserts on the formation of a stable HBc chimera is noted. However, it is also noted that Table 13 shows that Chimera 1569 V16.IA(M2)2C/2S yields 11.2 mg of particles, while its counterpart chimera 1789 V16(C48S/C107S).IA(M2)2C/2S yields 0.4 mg of particles. Since chimeras 1569 and 1789 share the same epitope peptide of IA(M2), and the only structural difference between chimera 1569 and 1789 is the substitutions of C48S/C107S in wt HBc, the instability of chimera 1789 does not appear to be due to epitope peptide inserts as Appellant argued.

26. Third, Appellant's arguments appear to contradict the Appellant's statement in Para 1, p.17 of the Appeal Brief, in which Appellant asserts that the evidence of Table 13 and Table 12 taken together "would reasonably convey to one skilled in the art that the Appellants had (in) possession of the claimed particles." However, if "the chimeras of Table 13 of the specification are not reflective of the current claims" as Appellant argued, how does Table 13 support the

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claim that Appellant was in possession of the claimed particles?

27. Importantly, the evidence in Table 13 and Table 12 of the specification shows several uncertainties in the ability of the claimed HBc chimers, which comprise substitutions of Cys48 and Cys107 and 5% mutation rate corresponding to wt HBc of SEQ ID NO: 1, to form stable particles. Specifically, Table 13 shows that there is no correlation between HBc Δ chimer comprising substitution of Cys48 and Cys107 and enhanced stability compared to HBc Δ chimer particles without substitution of Cys48 and Cys107. Table 13 shows that, like their counterparts of V16. β Am and V16.PA, Chimer 1794 V16(C48S/C107S). β Am; and Chimer 1780 V16(C48S/C107S).PA were not able to form particles. Chimer 1775 V16(C48S/C107S).ASP-1 has slightly better particle yield than, or about same as, its counterpart of V16.ASP-1. Chimer 1789 V16(C48S/C107S).IA(M2)2C/2S appeared to have less yield than its counterpart of chimer 1569 V16.IA(M2)2C/2S. Thus, Table 13 shows that there is no correlation between HBc Δ chimer comprising substitution of Cys48 and Cys107 and enhanced stability compared to HBc Δ chimer particles without substitution of Cys48 and Cys107. It is also noted that the Examiner's interpretation of the data in Table 13 is consistent with the teaching of the specification. As evidenced, the specification recites: "It should be noted, first, that all C48S/C107S epitope-carrying particles behaved in a manner similar to their wild type counterparts, signifying that these mutations did not affect particle assembly." See page 193, Para 3, of the specification (PG Pub Para [0506]).

28. Table 13 also shows that it is uncertain *which* mutation(s) in HBc core structure would lead to particles. Table 13 shows that mutations at amino acids A58 and L100; A69 and V89; W62 and F97, which contains less than "5% of the amino acids are substituted in the HBc chimer

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sequence corresponding to SEQ ID NO: 1", are not capable of forming particles.

29. Moreover, Table 12 shows that most HBc (C48S/C107S) chimeres have lower particle yields than HBc149 or HBc149+C (both of which contain cysteine residues at positions 48 and 107), except one HBc chimera HBc149(C48S/C107S)A69C/V89C+C.

30. Thus, the specification Example 14 shows it is not predictable in advance, which HBc variants would result in a stable HBc chimera. In other words, the specification has established there is a correlation between the arbitrary 5% mutation rate of HBc and ability of the mutated HBc to form particles. Importantly, Appellant's arguments have still failed to indicate *which* HBc chimeres in the specification would support the claimed HBc variants, which contain up to 5% mutations and would form stable HBc chimera particles. Thus, Appellant's arguments should not be found persuasive.

31. Appellant argues (3) that citing Metzger is irrelevant to a decision of whether the current claims satisfy the written description requirement. Metzger did not address chimeres having C-terminal cysteines and C48S/C107S substitution having enhanced stability as compared to those not having those limitations. Furthermore, one of skill in this art would find upon reading Metzger that proline 138 was important for particle formation and retain that amino acid.

32. This argument should not be found persuasive. Metzger is relevant to the claimed HBc chimera because it shows that modification of HBc protein can result in an unpredictable effect on the assembly of HBc particles. Consistent with the results shown in Table 13, Metzger shows that a single amino acid change, Pro138 to Gly, prevents self-assembly of the HBc protein into particles. Neither the art nor the specification has established that there is a correlation between HBc chimeres containing 5% substitutions in native HBc and their ability to form particles. The scope of the claims encompasses a large number of modified HBc variants. Although one of skill

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in this art would retain proline 138 of HBc, upon reading Metzger, he or she cannot envision which HBc containing a 5% substitution frequency in SEQ ID No: 1 would maintain its ability to form particles based on the knowledge of proline 138. Consequently, the skilled artisan would reasonably conclude Appellant was not in possession of the claimed HBc chimer particles containing a 5% substitution frequency of amino acid residues corresponding to wt HBc of SEQ ID NO: 1. Thus, Appellant's argument (3) should not be found persuasive.

II. Claims 1-47 fail to comply with the scope of enablement. The specification, while being enabling for a HBc chimer of SEQ ID NO: 1, does not reasonably provide enablement for a HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID No: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

33. Appellant argues that the term "corresponds" states that peptide sequences described contain only conservative substitutions along the polypeptide sequence. Appellant asserts that the specification describes and enables chimeric HBc molecules with conservative amino acid substitutions that retain biological activity and structural integrity. Appellant asserts that Fig. 1 describes several more examples of conservative substitutions in the various human viral strains. Moreover, In specific detail, the specification points out that the amino acid substitutions are to be up to 5% of the sequence, that the substitutions are to be conservative, that guidance as to proper conservative substitutions can be obtained with LASERGENE software and the like, and that the region of substitution is in the non-helical portion of the molecule, within residues 2-15 or 24-50, to assure particle formation. (Appeal Brief, pp.19-21)

34. These arguments should not be found to be persuasive. First, these arguments are based on the proposed or intended HBc chimers in the specification. However, the specification has not

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actually shown any HBc chimers, comprising 5% conservative substitutions, are able to form stable particles. Moreover, Appellant's assertion that "Fig. 1 describes several more examples of conservative substitutions in the various human viral strains" is not accurate. Fig. 1 shows amino acid sequences of **wild-type** of human HBc strains, Woodchucks and Ground Squirrel, which are *not* modified HBc variants comprising artificial 5% substitutions, or even 5% conservative substitutions of HBc. These wt HBc of different strains, or species are not examples of the claimed modified HBc variants comprising artificial 5% substitutions, or even 5% conservative substitutions of wt HBc. Rather, working examples of the specification show that it is not predictable which changes in wt HBc would maintain the ability of HBc to form particles, see discussion in Para 25-30 above. Thus, Appellant has not provided any factual evidence, either in the specification or in the art, that there is any correlation between artificial 5% substitutions, or even 5% conservative substitutions, of wt HBc and its ability to form HBc particles.

35. Moreover, a computer program, such as LASERGENE software, may help one of ordinary skill in the art to chose which amino acids could be altered, such general direction is not sufficient to predict the ability of said HBc chimera containing the proposed changes to form stable particles. This fact has been illustrated by the instant application. Although LASERGENE software appears to be readily available to the Appellant to "predict conservative substitutions of HBc, the software apparently did not assure particle formation of all HBc variants as shown by Table 14 of the specification. Thus, Appellant's argument without factual evidence should not be found persuasive.

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III. Claims 1-6, 8-14, 16-28, 30-42 and 46 are obvious over Pumpens, Zlotnick and Zhang.

36. Appellant presents seven arguments in traversal of this rejection. First, Appellant argues that Pumpens teaches away from the claimed invention because Pumpens teaches (a) that C-terminally truncated HBc (HBcΔ) is less stable than are the corresponding full-length HBc particles; (d) it is stated that elimination of 4 or 11 amino-terminal residues resulted in the complete disappearance of chimeric protein in *E. coli* cells (citing references 5 and 49); and (c) Table 1 of Pumpens shows that 25% of HBc constructs made were unable to assemble into capsid particles. Appellant asserts that this demonstration of poor capsid-forming ability and/or capsid instability illustrates that many chimeric particles would be poor candidates for vaccines and therefore teaches still further away from the present invention. (Appeal Brief; p. 24 and 25)

37. In response to argument (1), a prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Appellant." See In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). In present case, in contrast to Appellant's assertion of "teaching away" by Pumpens, the reference indicates that HBc has been successfully used as a foreign epitope carrier "because of its high-level production and correct self-assembly into naturally-shaped core particles" (see L. 8, col. 1; p. 63); "because of their increased immunogenicity, since they elicit a strong B-cell, T-cell and CTL response in primates and rodents" (see L.7-10, col. 2); and because of its "remarkable flexibility and unusually high capacity for acceptance of long foreign inserts" (see bridging sentence between p. 63 and 64). These art-recognized advantages of HBc, indicated by Pumpens, neither discourage nor are skeptical of developing HBc as vaccine carriers. Specifically, regarding Pumpens' teaching in Appellant's argument (a), recognizing the some problems of HBc as a vaccine carrier, such as the instability of HBcΔ particles, does not mean discouraging or being skeptical in making more stable HBc constructs. Rather, one of ordinary skill in the art recognized this

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specific problem of stability of HBcΔ, and was motivated to solve the problem. As evidenced, Page reference teaches that retention of the C-terminal cysteine in HBcΔ (lacking amino acids 150-180 of arginine repeats) to make a stable HBcΔ particle, see Page, Para 2, p.2. Thus, one of ordinary skill in the art, like Page and others cited in Pumpens reference was not discouraged.

38. Regarding Appellant's argument (b), Pumpen's teaching is recited below (Emphasis added):

“Replacement of 3 *N*-terminal amino acids with 8 *N*-terminal residues of cro protein from bacteriophage λ was also permitted [49] but elimination-of 4 [5] or 11 [49] *N*-terminal residues of HBc protein resulted in the complete disappearance of chimeric protein in *E. coli* cells. Therefore, some groups working on HBc protein engineering used only full-length carrier [35, 36, 50-59] or only C-terminally truncated variants HBc144 [60] or HBc 149 [61]; others tried to compare capabilities of full-length carriers and C-terminally truncated variants HBc144 [27, 37, 43a, 62-68] and HBc154 or HBc156 [69-73].

In view of the full text of the recitation above, Pumpens reported that while *N*-terminal-truncated HBc was reported unstable, but other groups use full-length of HBc or C-terminal-truncated HBc (HBcΔ). Since the instant claims are not directed to *N*-terminal truncated HBc, Pumpen's teaching regarding *N*-terminal truncated HBc does not constitute teaching away from the claimed invention. Rather, Pumpens' teaching provides guidance to one of ordinary skill in the art to use full-length or C-terminal-truncated HBc (HBcΔ) as platforms. Pumpens reference has also provided many examples in Tables 1-3, showing that full-length or HBcΔ is commonly used by one of ordinary skill in the art as epitope carriers.

39. Regarding Appellant's argument (c), indeed Table 1 shows about 25% of HBc constructs made were unable to assemble into capsid particles. However, in Tables 2 and 3, Pumpens shows that HBcΔ chimers can accommodate long foreign inserts, and have much higher success rates of particle assembly than that of full-length HBc in Table 1. In view of the success seen in the

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examples shown in Tables 1-3, one of ordinary skill in the art should not be discouraged from developing HBc Δ chimeras. It is also noted the HBc constructs were made by different research groups, see cited references. This evidence shows that one of ordinary skill in the art has not actually been discouraged from making HBc chimeras as Appellant asserted. Thus, Appellant's argument (1) should not be found persuasive.

40. Secondly, Appellant argues that Zlotnick teaches away from the inclusion of a C-terminal cysteine because Zlotnick emphasizes that there is no advantage in having a C-terminal cysteine in his gold-labeled molecules. Appellant asserts (a) that, in the Abstract, Zlotnick states that the HBc chimera having a cysteine at the 150 position that is bonded to a gold cluster is "unimpaired in its ability to form capsids." This teaches one of skill in the art that this molecule, although it has no free C-terminal cysteine, was able to form capsids. This teaches that the C-terminal cysteine is not important for capsid formation or stabilization and thus teaches away from the present claims. (b) Cp*149 has no cysteines yet still assembled into stable particle. Cp*150 in DTT, the reduced form, still assembled into stable particles. These facts also teach that the C-terminal cysteine is not important, and thus teach away from the present invention. (Appeal Brief, Para 1 and 2, p. 26)

41. Appellant's argument (2) should not be found persuasive because Appellant has misinterpreted Zlotnick's teaching. Appellant's argument (a) is based on speculation. When Zlotnick teaches that HBc150 labeled with a gold cluster "is unimpaired in its ability to form capsids", it simply means that gold-labeling HBc150 does not affect its ability to form an HBc particle. Zlotnick does not teach or imply that "the C-terminal cysteine is not important for capsid formation or stabilization" as Appellant asserted.

42. Regarding Appellant's argument (b), it was known that C-terminal truncated HBc without additional cysteine is capable of forming a particle, and was used for making HBc Δ chimeras; as evidenced by Pumpens; see Tables 2 and 3. However, it was also known in the art that HBc Δ is

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less stable as indicated by Pumpens (see Appellant's argument 1(a) in para 36 above). Here, Zlotnick explicitly teaches that a cysteine at the C-terminus of HBc150 help HBcΔ resist to capsid disassociation, and promote capsid formation, as shown in page 9558, col.1, paragraphs 1 and 2, *Results and Discussion*, as recited below (Underline emphasis added by the examiner):

“When reduced CP*150 capsids were stored without DTT for 2 days, >90% of the protein oxidized to form disulfide-bonded dimers (Fig. 2 *a*). These bonds stabilize the quaternary structure of the capsid, as attested by the observation that oxidized Cp*150 capsids—unlike CP*149 capsids or reduced Cp*150 capsids—are resistant to dissociation by 3.5 M urea (Fig. 2 *b*). Knowledge of the location of residue 150 (see below) indicates that this disulfide bond links two dimers (Fig. 1 *b*) and is distinct from the intradimeric disulfide observed in Cp proteins with native cysteines (16, 25).

Generally, when Cp proteins are stored in a low ionic strength, high pH buffer they do not polymerize (10). However, when stored in this buffer without DTT, Cp*150 dimers assemble into capsids, as determined by negative stain electron microscopy and analytical ultracentrifugation. A high proportion of the protein in these capsids is disulfide-bonded (Fig. 2 *a*). These data show that disulfide bond formation by Cp*150 can promote capsid assembly. Without disulfide formation, higher-order structures do not accumulate in storage buffer, i.e., the rate for dissociation is greater than the rate of association. Formation of these disulfide bonds stabilizes complexes against dissociation. Thus, under these conditions, Cp polymerization appears to involve an equilibrium between subunits, assembly intermediates, and capsids (36). We also note that, in capsids, the cysteine 150 residues from adjacent subunits must be close enough to one another to form a covalent bond, a distance of 4.6–7.4 Å between α carbons (37)”.

In view of the teachings recited above, one skilled in the art would conclude that Zlotnick explicitly teaches that Cp*150, which contains a C-terminal cysteine, plays a critical role in its particle assembly and stability. These facts would lead one skilled in the art to conclude that C-terminal cysteines are important for HBc capsid formation and stability.

43. Third, Appellant argues that Zlotnick used improper controls. Therefore, one of skill in the art would not conclude that C-terminal cysteines are responsible for capsid stabilization. Specifically, Appellant asserts that nowhere in the disclosure of Zlotnick are the **same two molecules made and analyzed, with the only difference being the existence of a C-terminal cysteine on one of the molecules**. Without such a model, one of skill in the art should not conclude that a C-terminal cysteine is stabilizing. Appellant asserts that because the length of

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the molecules is different, Cp*149 and Cp*150 are not a proper model system. (Appeal Brief, last Para, p. 26 to p. 28).

44. In response to this argument, Zlotnick's Cp*149 appears to be a proper and logical control for Cp*150 to examine the effect of the C-terminal cysteines of HBc because the Zlotnick manuscript is published in a peer-reviewed scientific journal. This fact indicates that one of ordinary skill (Reviewers) in the art has accepted the scientific evidence and conclusions presented in the Zlotnick manuscript.

45. In contrast to Appellant's argument, ironically, Appellant's specification has used the same logical controls as Zlotnick's to prove the stability effect of C-terminal cysteines of HBc, see e.g. Examples 13 and Table 12. Table 12 shows comparisons of HBc particle assembly, especially see HBc149 v. HBc149+C; HBc149(C48S/C107S) v. HBc149(C48S/C107S)+C; etc. More examples, the specification teaches comparison of the stability of C-terminally stabilized C48S/C107S chimera and its C48S/C107S counterpart; see page 192, para 1 of the specification (PG Pub Par [0501]). Here, Appellant's HBc149 does not appear to have the same length as HBc149+C; and HBc149(C48S/C107S) does not appear to have the same length as HBc149(C48S/C107S)+C. These comparisons exemplified in specification appear to be analogous to Zlotnick's comparison of Cp*150 vs. Cp*149. Thus, Appellant's argument against Zlotnick seems to contradict the teaching of the specification.

46. Since Appellant's argument (3) is not supported with evidence, it should not be found persuasive.

47. Forth, Appellant further argues that Figure 2b of Zlotnick refers to gold-cluster-labeled capsids, which the present claims do not recite. Therefore, it is not proper to rely on Figure 2b of Zlotnick as a factual basis for finding obviousness. (Appeal Brief, pp. 29 and 30)

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48. This argument should not be found persuasive. Here, Zlotnick teaches use of the gold-cluster-labeled HBc Δ for studying “the C-terminus of the assembly domain of HBc protein” by cryo-electron micrograph; see Title. It is common practice in the art of biology to study the function of a compound by using the labeled compound. Zlotnick specifically indicates that “The labeled protein is unimpaired in its ability to form capsid” (see Abstract, L.13 and 14). Fig. 2b shows the polymerized Cp*150 forms. Thus, Appellant’s argument against the gold-cluster-labeled HBc compound should not be found relevant.

49. Moreover, since the C-terminal cysteines(s) of HBc chimera is one of the structural features of the claimed chimera [e.g. Claim 1(2)], Zlotnick’s teaching regarding the effect of C-terminal cysteines is directly relevant to the claimed HBc chimera. Therefore, Appellant’s argument (4) should not be found persuasive.

49. Fifth, Appellant argues that Zlotnick suggests that other forces are at work besides cysteine binding in terms of capsid assembly. He states that binding of Au11 to Cp*150 induces capsid assembly. Therefore, one of skill in the art would not conclude that C-terminal cysteines are responsible for capsid stabilization, but rather the opposite, that they are not so important. (Appeal Brief, p. 31).

50. Appellant’s argument (5) is noted. However, this particular experiment, to which Appellant referred on page 9560, col. 2, first paragraph, is directed to assembly of Au11-labeled Cp*150, not Cp*150. In fact, Zlotnick illustrates that two different factors, C-termini Cys on HBc Δ and Au11, can influence HBc Δ assembly in two different experiments; see page 9558, col.1, para 1-3, *Results and Discussion*, under “Capsid Assembled from Cp*150 and Cp*150-Au11”. In first experiment, Zlotnick teaches that “bond formation by Cp*150 can promote

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capsid assembly” and “stabilizes complexes (capsid particle) against dissociation”; see the citation in Para 56 above (para 1 and 2; Id). This experiment by itself teaches that *C*-terminal cysteines are important for HBcΔ capsid formation and stability. In the second experiment, in addition, Zlotnick teaches that modification of Cp*150 with Au11 also promotes polymerization, see line 8 and 9, Para 3, left col. p.9558. Here, Zlotnick clearly illustrates two different factors, *C*-terminal Cys on HBcΔ and Au11, can influence HBcΔ assembly. However, just because Au11 can promote capsid assembly, it does not mean that the effect of *C*-terminal cysteines on HBc capsid formation and stability is not important. One of ordinary skill in the art would conclude that *C*-terminal cysteines are responsible and important for capsid stabilization, as evidenced by Page; see e.g. page 2 (also see para 13 above). Thus, Appellant’s argument should not be found persuasive.

51. Sixth, Appellant argues that any argument based on the effect of a *C*-terminal cysteine is not relevant to the claims such as claim 25 and its dependent claims, which require that the formed particles are more stable ... than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions 48 and 107. Thus, whether the *C*-terminal Cys is present or not present is irrelevant to these claims. (Appeal Brief, p. 32)

52. This argument should not be found pervasive. First, all claims require the claimed HBc chimer polymers (particles) comprising “one to three cysteines toward the *C*-terminus of the molecule from the *C*-terminal residue of the HBc sequence” [see e.g. Claim 1(2)]. Zlotnick teaches that *C*-terminal cysteines of HBcΔ can promote capsid assembly. Thus, Zlotnick’s teaching is relevant to the claimed chimer.

53. Secondly, “said chimer ... and being more stable on storage...than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions

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48 and 107” of Claim 25 indicates intended property of the claimed HBc chimera (which has been considered in Para 24-30 above), but not a structural limitation to the claimed chimera.

54. Interestingly, the specification teaches that “all C48S/C107S epitope-carrying particles behaved in a manner similar to their wild type counterparts, signifying that these mutations did not affect particle assembly”; see page 193, para 3 of the specification (PG Pub Para [0506].)

The specification, page 192, para 1 (PG Pub Para [0501]), is recited below:

“Significantly, all particles (except non-*C*-terminally stabilized controls) that were incubated at 37°C were entirely disulfide bonded after a period of 7 days. Of particular note was the fact that the *C*-terminally stabilized C48S/C107S chimera appeared to be entirely disulfide bonded at day zero, whereas its C48/C107 counterpart was not and did not reach the same level of cross-linking achieved by the C48S/C107S chimera during the period of study. Additionally, the engineered particle HBc149(C48S/C107S)W62C/F97C+C exhibited the same high level of cross-linking at day zero.”

In view of the citation above, the specification teaches that it is a *C*-terminal cysteine at HBcΔ, rather than substitution of C48S/C107S, that stabilizes the particle of HBc chimera. The results, shown on page 192, para 1 of the specification, are consistent with the teaching by Zlotnick, see Para 42 above. Thus, Appellant’s argument (6) should not be found convincing.

55. Seventh, Appellant argues that Zheng states that “disulfide bonds are not essential for core particle formation.” (See page 9422, Abstract, lines 13-14). Moreover, Zheng repeatedly stated that “[a]ll of the proteins [referring to two wild-type and 12 mutants] were shown to have very similar physical and immunochemical properties. All assemble into essentially identical core particle structures”, referring to size, charge, etc. (See Abstract, page 9422) (Appeal Brief, pp.32 and 33)

56. In response, the examiner notes Appellant’s quotation from Zheng. However, in addition, Zhang teaches that Cys 61 and Cys183(*C*-termini) are required for forming interchain disulfide bonds with another monomer, resulting in HBc dimers (see e.g. Abstract and Para 3, right col.

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and also see Figure 3). It is known that HBc dimer is basic unit to form HBc capsid particles, see e.g. Pumpens, L.1-8, left col. p. 64. (also see Para 7, above; and also see Zlotnick, Abstract and Fig. 2(b)) Zhang teaches: "A single mutation at Cys⁴⁸ produced only dimers with no detectable monomers (Figure 3, lane 3); mutation of Cys⁶¹ alone resulted in the production of both dimers and monomers (Fig.3, lane 4). ... mutations of both Cys⁴⁸ and Cys¹⁰⁷ results in only dimers (Para 3, right col. and also see Figure 3, lane 7) due to the disulfide bond between Cys⁶¹s" (see bridging para between pp. 9424 and 9425). By showing these results, Zhang teaches that Cys48 and Cys107 are not essential for formation of an interchain disulfide bond with another monomer because mutations of Cys48 and Cys107 do not affect formation of HBc dimers, while Cys61 is important for forming and maintaining an HBc dimer. Moreover, these results also illustrate that substitution of one or both Cys48 and/or Cys107 result in only HBc dimers, rather than a mixture of dimers and monomers (Para 2, right col. p. 9424, and Figure 3), which would have suggested to and motivated one of ordinary skill in the art to substitute one or both native Cys48 and Cys107, but maintain Cys61, [e.g. Claim 47 (a)] in order to obtain unified HBc dimers. In other words, the claimed chimera comprising substitutes of one or both Cys48 and Cys107 while maintaining Cys 61 is a "predictable use of prior art elements according to their established functions." KSR, page 13. Thus, Appellant's argument should not be found persuasive.

IV. Claims 1-6, 8-28, and 30-46 are obvious over Page, Birkett (6,231,864), and Zhang.

57. Appellant argues that (a) Page does not teach the substitution of cysteines 48 and 107; (b) Page does not teach the importance of the retention of cys61 as is present in the claimed chimeric particles; (c) Page does not teach the inclusion of an epitope at the N-terminus of the molecule. Therefore, the molecules of Page and the currently claimed molecules are very different. Therefore, Page is not relevant to the presently claimed molecules. Moreover, (d) Birkett does

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not teach substitution of cysteines 48 and/or 107 with another amino acid. (e) Birkett also does not address that adding a terminal cysteine lends stability to such a molecule. (f) Birkett teaches only full length HBc molecules. Appellant asserts that, when the skilled worker sums the teachings of the relied-on art, he/she does not know what to keep in and what to omit. The signposts are lacking. As a consequence, the present invention as a whole is not and was not *prima facie* obvious based on the combined teachings of this art. (Appeal Brief, pp.35 and 36)

58. In response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Specifically, regarding Appellant's argument (a) (b) and (d), Zhang has taught and suggested this limitation; See Para 10 and 56 above. Regarding to argument (c), Page teaches the inclusion of an epitope at the N-terminus of the molecule; See Page, last Para, p. 10. Page teaches: "There are three preferred regions for insertion of the epitopes, namely the C-terminus in place of deleted arginine repeat(s), the el loop and the N-terminus. These three regions all tolerate well insertion of foreign sequences." Regarding (e) and (f), Page teaches that "the C-terminal cysteine allows for the formation of a disulphide bond which in the native structure is important for the formation of a stable particle." (See page 2). Thus, the structural elements of the claimed chimera have been taught and suggested by the cited references.

59. One of ordinary skill in the art would have been motivated to modify HBc Δ by incorporating these features in order to improve the stability of HBc chimeras. There would have been reasonable expectation of success, given the knowledge that HBc Δ chimeras are capable of incorporating foreign epitope(s) at their N-terminal, immunodominant loop, or/and C-terminal region, and also capable of forming viral RNA-free capsid, as taught by Page, given the knowledge that addition/retention of C-terminal cysteines allows formation of a stable HBc Δ

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dimer particle as taught by Page, given the knowledge that HBc chimera containing a chemically-reactive linker residues for a conjugated hapten at their immunodominant loop have been successfully made, as taught by Birkett, and also given the knowledge that native Cys48 and Cys107 are not essential for HBc dimer formation, as taught by Zhang. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Therefore, Appellant's argument should not be found persuasive.

V. Claims 1-46 are obvious under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over (1) Claims 1-78 of 09/930,915; (2) Claims 1-53 of 10/787,734 (now US Pat. 7,361,352); (3) Claims 47-85 of 11/508,655.

60. Appellant acknowledges this rejection, but believes to be premature to deal with a terminal disclaimer at the present time.

VI. Claims 1-6, 8-28, and 30-46 were rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Page, *et al* (WO 01/98333 A2) and Zheng (J. Biological Chemistry, Vol. 267 (13): pp. 9922-9429, 1992)

61. Appellant acknowledges this rejection, but believes to be premature to deal with a terminal disclaimer at the present time.

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(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/BO PENG/

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